REMARKS

Claims 3-16 are pending in the application. Claims 6-11 are withdrawn from consideration. Claims 3-5 and 12-16 stand rejected. Applicant now addresses the Examiner's comments and claim rejections in the order presented in the office action to the extent that they might be applied to pending Claims 3-5 and 12-16.

Rejection under Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 3-5 and 12-16 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 8-15 of U.S. Patent No. 6,384,076. The Office Action indicates that a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome this rejection.

A Terminal Disclaimer to Obviate a Double Patenting Rejection over a Prior Patent and a Statement under 37 C.F.R. §3.73(b) signed by the assignee are being filed concurrently herewith. Accordingly, Applicant requests that this rejection of Claims 3-5 and 12-16 be withdrawn.

Rejection under 35 U.S.C. §102

Claims 3-5 and 12-16 stand rejected under 35 U.S.C. §102(b) as anticipated by Edmundson et al. (WO 98/13062). The Examiner contends that (1) Edmundson et al. discloses a method for treating various forms of arthritis such as rheumatoid arthritis by administering APM and alkyl derivatives; (2) Medline abstracts 90333175, 93088234 and 95072271 establish that patients with rheumatoid arthritis have higher or significantly higher blood viscosity, showing what would have been inherent in Edmundson et al's claims and disclosure; (3) Edmundson et al treated all rheumatoid arthritic patients and at least some of them must necessarily have had high whole blood viscosity or abnormally viscous whole blood; and (4) because the same patients were treated with APM and alkyl ester derivatives with the same dosage, the same therapeutic results (reduction in whole blood viscosity in a patient) must necessarily have been obtained, the claims in the present application are anticipated. Applicant traverses this rejection for reasons given below.

In WO 98/13062 at Page 18, line 23 through Page 23, line 34, Edmundson et al present data in transgenic mice (known to be a useful model for studying anti-TNF-α and other agents for treatment of RA) that indicate APM-treated mice experienced less loss of function, less joint swelling and apparently less vasculitis than the untreated controls. In no way does WO 98/13062

teach or suggest that APM is an effective treatment for high whole blood viscosity or abnormally viscous whole blood in an RA patient. Therefore, WO 98/13062 does not anticipate the present application.

For inherent anticipation, the claimed element necessarily must always be found in the composition or result in the process disclosed in the cited prior art reference. Inherency may not be based on possibilities. The Federal Circuit addressed anticipation issues in Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 20 USPQ 2d 1746 (Fed.Cir. 1991). In discussing the anticipation by inherency doctrine, the court stated:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . . Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. . . . If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, seems to be well settled that the disclosure should be regarded as sufficient.

Continental Can, 948 F.2d at 1268-69.

In order for Edmundson et al to inherently anticipate the present application, it requires that *every* patient treated for rheumatoid arthritis (hereinafter "RA") according to the method of Edmundson et al would have the condition of high whole blood viscosity or abnormally viscous blood. Applicant submits that not all RA patients have high whole blood viscosity or abnormally viscous blood. Moreover, the references cited in the office action do not support the possibility that all RA patients have high whole blood viscosity or abnormally viscous blood.

Balabanova et at (Medline Accession No. 90333175) discloses a study of RA patients with systemic manifestations and high laboratory activity. In particular, the hyperviscosity of the blood in patients with systemic manifestations was linked to the presence of pathological immune complexes in the blood. This study concentrated on one particular subgroup of RA patients (i.e., patients with systemic manifestations, e.g., rheumatoid nodules, rheumatoid vasculitis, and ocular, respiratory, cardiac, hematologic, and neurologic complications); it did not include other types of RA patients such as those experiencing oligoarticular illness of brief duration. From this study, a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood.

Sundukov et al (Medline Accession No. 93088234) also discloses a study of RA patients with systemic manifestations. As discussed above, since this study only included patients with systemic manifestations, a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood.

Gudmundsson et al (Medline Accession No. 95072271) discloses a study of different methods of measuring whole blood viscosity using a couette rotational viscometer for the purpose of developing a method of testing the blood samples of RA patients to best differentiate between the viscosities of RA patients and healthy controls. Gudmundsson et al discloses a specific method by which native or whole blood viscosity, corrected blood viscosity, plasma viscosity and red cell aggregation were all significantly higher in the RA patients tested than in controls. Gudmundsson et al does not specify the types of patients involved in this particular study; however, given that the purpose of this study was to maximize the differences between the whole blood viscosity levels of RA patients and controls, it would seem reasonable that Gudmundsson et al would have selected patients known to have high whole blood viscosity. In no way does Gudmundsson et al indicate that his study included patients representative of all types of RA patients or that his test results are representative of *all* RA patients.

Reported laboratory findings for RA indicate a consensus that while no tests are specific for diagnosing the disease, blood tests can be helpful (copies attached at **Tab A** and **Tab B**: *Harrison's Principles of Internal Medicine*, 14th ed., AS Fauci, E Braunwald, KJ Isselbacher, JD Wilson, JB Martin, DL Kasper, SL Hauser, and DL Longo, eds., McGraw-Hill, New York, New York; 1998, vol. II, p. 1884; and The Merck Manual, 16th ed., R Berkow and AJ Fletcher, eds., Merck & Co., Inc., Rahway, New Jersey; 1992, p. 1306). Exemplary blood tests include the presence of normochromic-normocytic anemia and/or thrombocytosis, elevated erythrocyte sedimentation rate (ESR), elevated plasma viscosity, presence of rheumatoid factor, and elevated acute phase reactants such as ceruloplasmin and C-reactive protein. Elevated ESR was noted in 90% of active RA cases; however, increased sedimentation of red blood cells is not indicative of increased whole blood viscosity. Likewise, elevated plasma viscosity was considered equally sensitive to elevated ESR; however, plasma viscosity is not indicative of whole blood viscosity. High whole blood viscosity or abnormally viscous blood were not listed in these as being diagnostic of RA. Moreover, Bull et al reported a consensus analysis devised to assess the performance of 31 laboratory tests commonly used to monitor acute and chronic inflammatory

diseases, and in 17 RA patients, plasma viscosity and ESR (reportedly found in 90% of RA patients with acute disease) were ranked in first place and the measurement of acute-phase serum protein orosomucoid ranked third as being the most useful tests (Bull, et al. 1986. "Ranking of laboratory tests by consensus analysis," *Lancet* 2:377-380; abstract at **Tab C**). High whole blood viscosity and abnormally viscous blood did not rank as one of the top three tests, providing further evidence that these conditions are not always found in RA patients.

In summary, there are enough conflicting reports about laboratory findings in RA patients to show that a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood or that it would represent proof of disease. Nor would a person skilled in the art conclude from the teachings of WO 98/13062 that treatment of RA with APM and/or its derivatives would result in lowering high whole blood viscosity or abnormally viscous blood. In Example 5 of WO 98/13062, Applicant presents data that show APM and/or derivatives lowering the deleterious effects of TNFα in transgenic mice accepted as an animal model for studying RA. It is also well known in the art that bone loss is associated with RA; and WO 98/13062 discloses APM and/or derivatives decreasing synovial swelling, bone thickening tenderness after 6 months treatment and decreasing bone readsorption after 15 months treatment in an RA patient (Page 16, lines 18-30). Thus, based on WO 98/13062, a person skilled in the art would recognize the benefits of treatment with APM and/or derivatives for RA to include reduction in TNFα effects and bone loss, and not use of APM and/or derivatives to reduce high whole blood viscosity or abnormally viscous blood.

For the foregoing reasons, Applicant believes that pending Claims 3-5 and 12-16 are not inherently anticipated by WO 98/13062 and respectfully requests that this rejection of these claims be withdrawn.

Applicant does not believe that any fee is required for this amendment. However, if this is error, please charge any necessary fee to Sidley Austin Brown & Wood LLP's Deposit Account No. 18-1260.

Respectfully submitted,

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KLK:jkk

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singly or in clusters. When they appear in individuals with pneumoconiosis, a diffuse nodular fibrotic process (Caplan's syndrome) may develop. On occasion, pulmonary nodules may cavitate and produce a pneumothorax or bronchopleural fistula. Rarely, pulmonary hypertension secondary to obliteration of the pulmonary vasculature occurs. In addition to pleuropulmonary disease, upper airway obstruction from cricoarytenoid arthritis or laryngeal nodules may develop.

Clinically apparent heart disease attributed to the rheumatoid process is rare, but evidence of asymptomatic pericarditis is found at autopsy in 50 percent of cases. Pericardial fluid has a low glucose level and is frequently associated with the occurrence of pleural effusion. Although pericarditis is usually asymptomatic, on rare occasions death has occurred from tamponade. Chronic constrictive pericarditis also may occur.

RA tends to spare the central nervous system directly, although vasculitis can cause peripheral neuropathy. *Neurologic manifestations* also may result from atlantoaxial or midcervical spine subluxations. Nerve entrapment secondary to proliferative synovitis or joint deformities may produce neuropathies of median, ulnar, radial (interosseous branch), or anterior tibial nerves.

The rheumatoid process involves the *eye* in fewer than 1 percent of patients. Affected individuals usually have long-standing disease and nodules. The two principal manifestations are episcleritis, which is usually mild and transient, and scleritis, which involves the deeper layers of the eye and is a more serious inflammatory condition. Histologically, the lesion is similar to a rheumatoid nodule and may result in thinning and perforation of the globe (scleromalacia perforans). Fifteen to twenty percent of persons with RA may develop Sjögren's syndrome with attendant keratoconjunctivitis sicca.

Felty's syndrome consists of chronic RA, splenomegaly, neutropenia, and on occasion anemia and thrombocytopenia. It is most common in individuals with long-standing disease. These patients frequently have high titers of rheumatoid factor, subcutaneous nodules, and other manifestations of systemic rheumatoid disease. Felty's syndrome is very uncommon in African Americans. It may develop after joint inflammation has regressed. Circulating immune complexes are often present, and evidence of complement consumption may be seen. The leukopenia is a selective neutropenia with polymorphonuclear leukocyte counts of less than 1500 cells per microliter and sometimes less than 1000 cells per microliter. Bone marrow examination usually reveals moderate hypercellularity with a paucity of mature neutrophils. However, the bone marrow may be normal, hyperactive, or hypoactive; maturation arrest may be seen. Hypersplenism has been proposed as one of the causes of leukopenia, but splenomegaly is not invariably found and splenectomy does not always correct the abnormality. Excessive margination of granulocytes caused by antibodies to these cells, complement activation, or binding of immune complexes may contribute to granulocytopenia. Patients with Felty's syndrome have increased frequency of infections usually associated with neutropenia. The cause of the increased susceptibility to infection is related to the defective function of polymorphonuclear leukocytes as well as the decreased number of cells.

Osteoporosis secondary to rheumatoid involvement is common and may be aggravated by glucocorticoid therapy. Glucocorticoid treatment may cause significant loss of bone mass, especially early in the course of therapy, even when low doses are employed. Osteopenia involves both juxtaarticular bone and long bones distant from involved joints. RA is associated with a modest decrease in mean bone mass and a moderate increase in the risk of fracture. Bone mass appears to be adversely affected by functional impairment and active inflammation, especially early in the course of the disease.

RA in the Elderly The incidence of RA continues to increase past age 60. It has been suggested that elderly onset RA might have a poorer prognosis, as manifested by more persistent disease activity, more frequent radiographically evident deterioration, more frequent systemic involvement, and more rapid functional decline. Aggressive disease is largely restricted to those patients with high titers of rheumatoid factor. By contrast, elderly patients who develop RA without elevated titers of rheumatoid factor (seronegative disease) generally have less severe, often self-limited disease.

LABORATORY FINDINGS No tests are specific for diagnosing RA. However, rheumatoid factors, which are autoantibodies reactive with the Fc portion of IgG, are found in more than two-thirds of adults with the disease. Widely utilized tests largely detect IgM rheumatoid factors. The presence of rheumatoid factor is not specific for RA. Rheumatoid factor is found in 5 percent of healthy persons. The frequency of rheumatoid factor in the general population increases with age, and 10 to 20 percent of individuals over 65 years old have a positive test. In addition, a number of conditions besides RA are associated with the presence of rheumatoid factor. These include systemic lupus erythematosus, Sjögren's syndrome, chronic liver disease, sarcoidosis, interstitial pulmonary fibrosis, infectious mononucleosis, hepatitis B, tuberculosis, leprosy, syphilis, subacute bacterial endocarditis, visceral leishmaniasis, schistosomiasis, and malaria. In addition, rheumatoid factor may appear transiently in normal individuals after vaccination or transfusion and also may be found in relatives of individuals with RA.

The presence of rheumatoid factor does not establish the diagnosis of RA but can be of prognostic significance because patients with high titers tend to have more severe and progressive disease with extraarticular manifestations. Rheumatoid factor is uniformly found in patients with nodules or vasculitis. The predictive value of the presence of rheumatoid factor in determining a diagnosis of RA is poor. Thus fewer than one-third of unselected patients with a positive test for rheumatoid factor will be found to have RA. The test is not useful as a screening procedure but can be employed to confirm a diagnosis in individuals with a suggestive clinical presentation and, if present in high titer, to designate patients at risk for severe systemic disease.

Normochromic, normocytic anemia is frequently present in active RA. It is thought to reflect ineffective erythropoiesis; large stores of iron are found in the bone marrow. In general, anemia and thrombocytosis correlate with disease activity. The white blood cell count is usually normal, but a mild leukocytosis may be present. Leukopenia also may exist without the full-blown picture of Felty's syndrome. Eosinophilia, when present, usually reflects severe systemic disease.

The erythrocyte sedimentation rate is increased in nearly all patients with active RA. The levels of a variety of other acute phase reactants including ceruloplasmin and C-reactive protein are also elevated, and generally such elevations correlate with disease activity and the likelihood of progressive joint damage.

Synovial fluid analysis confirms the presence of inflammatory arthritis, although none of the findings is specific. The fluid is usually turbid, with reduced viscosity, increased protein content, and a slightly decreased or normal glucose concentration. The white cell count varies between 5 and 50,000 cells per microliter; polymorphonuclear leukocytes predominate. A synovial fluid white blood cell count of more than 2000 cells per microliter with more than 75 percent polymorphonuclear leukocytes is highly characteristic of inflammatory arthritis, although not diagnostic of RA. Total hemolytic complement, C3, and C4 are markedly diminished in synovial fluid relative to total protein concentration as a result of activation of the classic complement pathway by locally produced immune complexes.

RADIOGRAPHIC EVALUATION Early in the disease, roentgenograms of the affected joints are usually not helpful in establishing a diagnosis. They reveal only that which is apparent from physical examination, namely, evidence of soft tissue swelling and joint effusion. As the disease progresses, abnormalities become more pronounced, but none of the radiographic findings is diagnostic of RA. The diagnosis, however, is supported by a characteristic pattern of abnormalities, including the tendency toward symmetric involvement. Juxtaarticular osteopenia may become apparent within weeks of onset. Loss of articular cartilage and bone erosions develop after months of sustained activity. The primary value of radiography is to determine the extent of cartilage destruction and bone erosion produced by the disease, particularly when one is monitoring the impact of therapy

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interleukin-2, other kinins, rheumatoid factor (**RF**) and other immunoglobulins. Fibrin deposition, fibrosis, and necrosis also are present. These findings are typical but not diagnostic. Hyperplastic synovial tissue (pannus) may erode cartilage, subchondral bone, articular capsule, and ligaments. Polymorphonuclear leukocytes are not prominent in the synovium but often predominate in the synovial fluid.

The **rheumatoid nodule**, seen in 30 to 40% of patients and usually found subcutaneously at sites subject to trauma, is the most characteristic pathologic lesion. It is a nonspecific necrobiotic granuloma consisting of a central necrotic area surrounded by "palisaded" mononuclear cells with their long axes radiating from the center, all enveloped by lymphocytes and plasma cells. Nodules and **vasculitis** have been found at necropsy in many visceral organs in severe cases of RA but are clinically significant in only a few cases.

Symptoms and Signs

Onset may be abrupt, with simultaneous inflammation in multiple joints, or (more frequently) insidious, with progressive joint involvement. Tenderness in nearly all "active" (inflamed) joints is the most sensitive physical sign. Synovial thickening, the most specific physical finding, eventually occurs in most active joints. Symmetric involvement of small hand joints (especially proximal interphalangeal and metacarpophalangeal), feet (metatarsophalangeal joints), wrists, elbows, and ankles is typical; but initial manifestations may occur in any joint. Stiffness lasting > 30 min on arising in the morning or after prolonged inactivity is common; early afternoon fatigue and malaise also occur. Deformities, particularly flexion contractures, may develop rapidly. Ulnar deviation of the fingers with slippage of the extensor tendons off the metacarpophalangeal joints is typical. The carpal tunnel syndrome can result from wrist synovitis. Ruptured popliteal cysts can mimic deep venous thrombosis.

Subcutaneous rheumatoid nodules, though not usually an early manifestation, can be a major aid in diagnosis. Visceral nodules, vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, lymphadenopathy, Sjögren's syndrome, and episcleritis are other extra-articular manifestations. Fever may be present and is usually low-grade, except in the adult-onset **Still's disease**, a seronegative RA-like polyarthritis with prominent systemic features (see also JUVENILE RHEUMATOID ARTHRITIS in Ch. 200).

Laboratory and X-ray Findings

A normochromic (or slightly hypochromic)-normocytic anemia, typical of other chronic diseases, is found in 80% of cases; the Hb is usually > 10 gm/dL but may rarely be as low as 8 gm/dL. Superimposed iron deficiency or other causes of anemia should be sought if the Hb is < 10 gm/dL. Neutropenia is found in 2% of cases, often with splenomegaly (**Felty's syndrome**). Mild polyclonal hypergammaglobulinemia and thrombocytosis may be present.

The ESR is elevated in 90% of cases. Antibodies to altered γ-globulin, the so-called **rheumatoid factors (RFs)**, as detected by agglutination tests (eg, the latex fixation test) that show IgM RF, are found in about 70% of cases. Though RFs are not specific for RA and are found in many diseases (including granulomatous diseases, chronic liver disease, and SBE), a high RF titer provides helpful confirmation when the typical clinical syndrome is present. The **latex** and **bentonite tube dilution tests**, utilizing human IgG adsorbed to particulate carriers such as latex or bentonite, are less specific but more sensitive than the sensitized sheep cell test using rabbit IgG. In most laboratories, a latex fixation tube dilution titer of 1:160 is considered the lowest positive value favoring a diagnosis of RA. A very high RF titer suggests a worse prognosis and is often associated with progressive disease, nodules, vasculitis, and pulmonary involvement. The titer can be influenced by treatment or spontaneous improvement and often falls as inflammatory joint activity decreases.

The **synovial fluid**, abnormal during active joint inflammation, is cloudy and sterile, has reduced viscosity, and usually contains 3000 to 50,000 WBCs/μL. Polymorphonuclear

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1: Lancet. 1986 Aug 16;2(8503):377-80.

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Ranking of laboratory tests by consensus analysis.

Bull BS, Levy WC, Westengard JC, Farr M, Smith PF, Apperley JF, Bacon PA, Stuart J.

A new analytical technique (consensus analysis) was devised to assess the performance of laboratory tests that are commonly used to monitor the acute and chronic phases of inflammatory disease. On thirty-one tests carried out monthly for 7 months in seventeen patients with rheumatoid arthritis, the consensus analysis procedure ranked plasma viscosity and erythrocyte sedimentation rate in a tie for first place. Measurement of the acute-phase serum protein orosomucoid ranked third. Consensus analysis has the potential to reduce laboratory costs by identifying the most useful tests; it also promises to be helpful in the design of new laboratory tests that are more sensitive and specific.

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